

Long-Term Reproducibility of Electrophysiologically Guided Therapy With Sotalol in Patients With Ventricular Tachyarrhythmias

Christian Mewis, MD, Volker Kühlkamp, MD, Johann Mermi, MD, Ralph F. Bosch, MD, Ludger Seipel, MD
Tübingen, Germany

- OBJECTIVES** Goal of this study was to assess the long-term reproducibility of electrophysiologic drug testing in patients with ventricular tachyarrhythmias (VT/VF).
- BACKGROUND** Programmed ventricular stimulation (PVS) is still widely used to guide antiarrhythmic therapy in patients with sustained ventricular tachycardia/fibrillation (VT/VF). Sotalol is considered as one of the most effective drugs for VT/VF. Because there is no proof of long-term reproducibility of a successful drug test with sotalol, we investigated the long-term reproducibility of drug testing with sotalol.
- METHODS** Thirty patients with VT/VF (age: 57 ± 11 years, 20 patients with coronary heart disease, 7 patients with no structural heart disease, 3 with others) and reproducible induction of VT/VF (28 patients VT, two patients VF) in a baseline PVS, were suppressible with sotalol (mean dosage 395 ± 137 mg) in a subsequent PVS. After a mean follow-up of 13 ± 10 months a PVS was again performed in patients, who had no evidence of progressive cardiac disease, who did not experience any arrhythmia recurrences or who were drug compliant. Irrespective of the inducibility after long-term therapy with sotalol, all patients were kept on the initial sotalol regimen. All 30 patients had a stable cardiac condition, were free of VT/VF recurrences and were drug compliant.
- RESULTS** Despite the clinical efficacy of sotalol, in 12 patients (40%) VT/VF could again be induced after 13 ± 10.2 months. Inducibility was independent of age, heart disease, ejection fraction and follow-up time. During a further follow-up of 22.1 ± 10.9 months, five patients experienced nonfatal VT recurrences independently of the prior inducibility.
- CONCLUSIONS** This study shows a lacking long-term reproducibility of an initial effective PVS with sotalol. Despite an uneventful clinical follow-up, late electrophysiologic testing showed a VT/VF inducibility in a high portion of patients. Hence, electrophysiologic testing performed late after the initial drug test may no longer be predictive of outcome. (J Am Coll Cardiol 1999; 33:1989-95) © 1999 by the American College of Cardiology

Despite the increasing number cardioverter-defibrillator implantations, programmed ventricular stimulation (PVS) is still widely used to guide antiarrhythmic therapy in patients with sustained ventricular tachycardia/fibrillation (VT/VF). Accordingly, serial drug testing was crucial for the patient recruitment in the AVID and MADIT trials (1,2).

Sotalol is considered as one of the front-line antiarrhythmic drugs for the treatment of VT/VF because it turned out to be superior to various class I agents in the ESVEM trial (3). The efficacy of sotalol has been shown in many studies

before, which have relied on the guidance by electrophysiologic (EP) testing (4-10). An essential prerequisite for drug testing is the short- and long-term reproducibility of the baseline stimulation and of the drug test itself. Although the immediate reproducibility of VT/VF was described as fairly reliable (11-13), the day-to-day reproducibility was subjected to a variability ranging from 56% to 80% (11,14-16). The long-term reproducibility of VT/VF inducibility seems even more problematic (17). Hence, the few studies available reported a high short-term variability in terms of VT/VF suppression of serial drug tests (18-20). No study has so far addressed the long-term reproducibility of VT/VF suppression by antiarrhythmic drugs. Because a high variability of drug tests means a possible underestimation of the clinical efficacy of the tested substance, the purpose of this

From the Department of Cardiology, University Hospital Tübingen, Tübingen, Germany.

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Abbreviations and Acronyms

- CL = cycle length
- EP = electrophysiologic
- ICD = implantable cardioverter-defibrillator
- PVS = programmed ventricular stimulation
- SCD = sudden cardiac death
- VF = sustained ventricular fibrillation
- VT = sustained ventricular tachycardia

study was to assess the long-term reproducibility of initial successful EP study with sotalol in patients with VT/VF. All patients had to have a stable underlying heart disease and had to be free of VT/VF recurrences during the follow-up. Similar to the "parallel approach," as suggested by Brugada and Wellens, irrespective of inducibility in the EP study after long-term therapy with sotalol, the drug was continued and patients were further observed for relapses to establish the clinical significance of the long-term reproducibility of VT/VF suppression with sotalol (21,22).

METHODS

Study design. Patients with a history of VT/VF and suppressible VT/VF by sotalol (EP study 1 and 2) were reinvestigated after follow-up of at least six months (EP study 3), who were free of VT/VF recurrences and showed stable cardiac conditions and were drug compliant (Fig. 1).

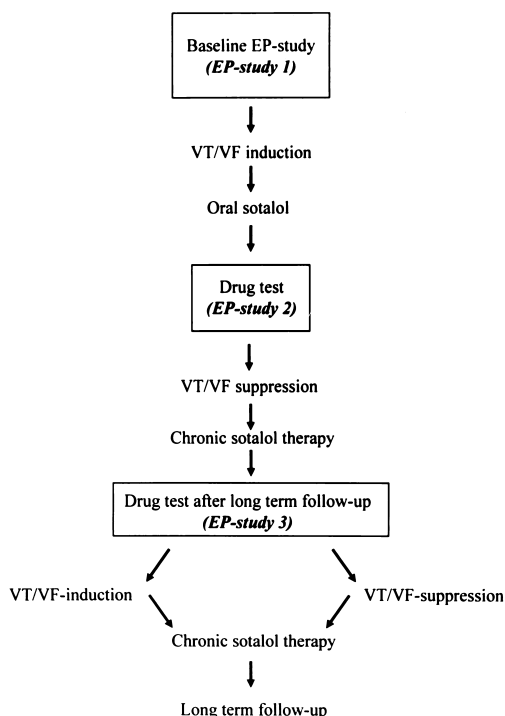


Figure 1. Study design. EP = electrophysiologic; VT/VF = sustained ventricular tachycardia/fibrillation.

Regardless of the inducibility in EP study 3, the identical sotalol regimen was maintained. The incidence of VT/VF or sudden cardiac death (SCD) was determined during a further follow-up and set in correlation to the arrhythmia inducibility in the prior EP study 3.

Patient selection, inclusion and exclusion criteria. From January 1992 to January 1997, 195 patients with VT/VF were inducible in a baseline PVS and tested with sotalol in a subsequent EP study. Seventy-eight consecutive patients (age 60 ± 12 years, 12 women and 66 men) were completely suppressible. Each patient was worked up, including coronary angiography, left ventriculography, echocardiography and exercise testing and, if considered necessary, right ventriculography. The identified heart disease was in 40 patients coronary heart disease, in 4 right ventricular dysplasia, in 17 dilated cardiomyopathy and in 1 valvular heart disease. In 16 patients, no structural heart disease could be identified. The mean left ventricular ejection fraction of all sotalol-responders was calculated at $40 \pm 15\%$. The arrhythmia history was in 16 patients SCD and in 62 monomorphic VT. Criteria excluding the use of sotalol were as follows: hemodynamic intolerance, severe renal insufficiency, symptomatic bradycardia or hypotension, asthma or chronic obstructive pulmonary disease, atrioventricular conduction disturbances or prolonged QT interval. All patients were reinvestigated after a follow-up of at least six months if they were drug compliant during the entire follow-up. Arrhythmia recurrence like aborted SCD, palpitations, syncope or documented VT, as well as deterioration of the cardiac status, led to the exclusion of the patient. After the follow-up period, echocardiography and exercise testing were repeated and compared with those initially performed. If the clinical history and the results of the noninvasive tests were suggestive of a progressive cardiac disease, the patient was excluded from the study.

The following reasons led to the exclusion of 48 patients (61%): 13 patients experienced nonfatal VT/VF recurrences during sotalol therapy, 5 patients died during follow-up (3 due to SCD, 2 due to extracardial diseases), 2 patients showed nonsustained torsade de pointes tachycardias during sotalol treatment, 13 patients had a deterioration of the cardiac disease (necessitating hospital admission in all patients), 10 patients did not tolerate sotalol therapy, 1 patient was lost for follow-up and 4 patients did not give informed consent. Hence, the remaining 30 patients completed the whole study (see Table 1 for patients characteristics); all of them were treated with sotalol in a mean dosage of 395 ± 137 mg. Drug compliance was assured in 18/30 patients taking plasma samples at the time of the EP study 3 for determination of sotalol plasma levels with high performance liquid chromatography.

Electrophysiologic study. All EP studies were performed with patients in the fasting, nonsedated state after they had given written informed consent. A baseline study was carried out after all antiarrhythmic drugs had been discon-

Table 1. Patient Characteristics and VT/VF Inducibility After Long-Term Sotalol Therapy

	Noninducibility of VT/VF (n = 18)	Reinducibility of VT/VF (n = 12)	p Value
Age (yr)	55.8 ± 2.8	59.4 ± 2.7	0.39
Cardiac disease	CAD = 10 patients RV dysplasia = 1 patient Idiopathic = 5 patients DCM = 2 patients	CAD = 10 patients RV dysplasia = 1 patient Idiopathic = 1 patient	0.19*
Primary arrhythmia	VT = 15 patients VF = 3 patients	VT = 8 patients VF = 4 patients	0.39
EF (%)	48.7 ± 3.7	42.9 ± 3.9	0.3
Sotalol dosage (mg)	364 ± 32	440 ± 40	0.14
Follow-up (mo)	13 ± 9.5 (median 6.5)	13 ± 10.2 (median 6.5)	0.98

*p was calculated for comparison of CAD patients.
 CAD = coronary artery disease; DCM = dilative cardiomyopathy; EF = ejection fraction; RV = right ventricular; VT/VF = sustained ventricular tachycardia/fibrillation.

continued for ≥5 half-lives, using conventional techniques of intracardiac recording and stimulation as has been previously reported (23). The PVS included four basic drive cycle lengths (CLs) (500, 430, 375 and 330 ms) with up to double extrastimuli. A third extrastimulus was then delivered at all four drive CLs. If necessary the protocol was repeated with a catheter placed in the right ventricular outflow tract and eventually subsequent orciprenaline infusion. Each extrastimulus was delivered at an initial coupling time of 350 ms (in the case of 330-ms basic drive CL 320 ms), which was reduced in 10-ms decrements until ventricular refractoriness occurred or to a coupling time not below 150 ms. The end point of our protocol was the induction of the clinical arrhythmia (i.e., reproducible induction of sustained VT in patients with a history of sustained VT or aborted SCD or induction of VF in patients with aborted SCD only).

Definitions. Sustained ventricular tachycardia was defined as ventricular tachycardia that lasted >30 s or was hemodynamically intolerable and needed termination before 30 s. Ventricular tachycardia was considered nonsustained if it terminated spontaneously within 30 s. Sustained ventricular fibrillation was defined as being polymorphic with a cycle length below 200 ms.

Efficacy criteria of the EP study with sotalol (EP study 2 and 3). After completion of dose titration of oral sotalol and a minimum of 72 h of administration of the final dose, EP testing was repeated. The PVS protocol and the end points were identical to those used at the baseline investigation. In all patients during each test, three extrastimuli with basic drive CL of 500 ms were utilized, unless VT or VF was induced with fewer extrastimuli or the VT/VF induction in the baseline stimulation required three extrastimuli with a basic drive CL of 430, 375 or 330 ms. If so, the protocol was completed by 330S4. Long-term therapy with sotalol was used in those patients whose VT/VF was either rendered noninducible or rendered nonsustained. The latter criterion was only applicable to one patient.

After long-term therapy with sotalol, the same stimulation protocol was performed in each patient using the same efficacy criteria (EP study 3).

Follow-up. All patients were followed up at three month intervals up to the EP-study 3. Afterwards the patients were seen also in three month intervals, after one year follow-up at yearly intervals in an outpatient clinic. Primary end points were the occurrence of VT/VF, unexplained syncope, SCD or discontinuation of sotalol. In patients with VT/VF relapses after EP-study 3 the same non-invasive tests were performed as before.

Data analysis. All values are expressed as mean ±1 standard deviation. Univariate analysis was performed with the non-paired two-tailed *t* test. Group comparison was done by using Fisher's exact test or the chi-square test where appropriate. A p value < 0.05 was considered statistically significant. Kaplan-Meier survival analysis with the log-rank test was used to report the estimates for the occurrence of study end points during follow up.

RESULTS

Baseline EP-study and subsequent EP-study with sotalol (EP study 1 & 2). As required for the inclusion into the study, in all 30 patients VT/VF could be induced. In patients with aborted SCD a monomorphic VT was induced with 2 extrastimuli in 4 patients and with 1 extrastimulus in 1 patient with a mean CL of 225 ms ± 25 ms. In the other 2 patients with SCD, VF was induced utilizing 2 and 3 extrastimuli, respectively. The remaining patients with a history of VT showed a reproducible induction of monomorphic VT utilizing 1 extrastimulus in 4, 2 extrastimuli in 13 and 3 extrastimuli in 6 patients. The mean CL of the induced VT was 310 ± 45 ms. For VT induction stimulation with 2 extrastimuli at the right ventricular outflow tract during orciprenaline infusion was required in 2 patients (1 without structural heart disease, one with dilated

Table 2. Number of Extrastimuli Required to Induce VT/VF in the Baseline EP Study 1 and After Long-Term Sotalol Therapy (EP Study 3)

EP Study 3	Baseline EP Study 1						
	500S2	500S2S3	430S2	430S2S3	375S2S3	330S2S3	500S4
500S2						Less difficult to induce VT/VF in sotalol EP study 3	
500S2S3	1						
430S2			1*	1			
430S2S3							
375S2S3		1			1*		
330S2S3	More difficult to induce VT/VF in sotalol EP study 3				1	1*	
500S4						2	1*
430S4			1				1

*The same number of extrastimuli was required to induce VT/VF in the baseline EP study and in the late EP study 3. The numbers in the table correspond to the number of patients who had inducible arrhythmias in response to the programmed stimulation sequence shown. For example, one patient, shown in the first column of the table, had inducible VT/VF in response to a single extrastimulus during a drive train of 500 ms during baseline EP testing, but required two extrastimuli during late EP retesting while treated with sotalol.

EP = electrophysiologic; VT/VF = sustained ventricular tachycardia/fibrillation.

cardiomyopathy). In all but one patient sotalol (mean dose of 395 ± 137 mg) prevented completely the induction of VT/VF in the subsequent drug test. In one patient, ventricular tachycardia was rendered more difficult to induce and was nonsustained.

Status of underlying heart disease. After a mean follow-up of 13 ± 10 months (median 6.5 months, range 6 to 36 months) all 30 patients were readmitted for electrophysiologic reevaluation. All patients denied new symptoms such as angina pectoris, dyspnea and palpitations which would have been suggestive of a progress of the cardiac disease or for arrhythmia recurrence. Exercise tests and echocardiography were performed and compared with the tests performed during the prior hospital stay. A significant reduction in left ventricular function or exercise capacity was not found in any of the patients.

Drug compliance and sotalol plasma levels. Sotalol plasma levels were taken at the beginning of the PVS (before 12:00 AM) and were available in 18 patients. The mean plasma level was determined with 2.2 ± 1.5 $\mu\text{g/ml}$ (therapeutic range: 1 to 3 $\mu\text{g/ml}$); all patients showed plasma levels within the therapeutic range. The local physicians and the follow-up outpatient visits assured drug compliance in all remaining patients.

Electrophysiologic study during long-term sotalol therapy (EP study 3). After 13 ± 9.5 months (median 6.5 months, range 6 to 36 months) of sotalol therapy in 18 patients again no VT/VF was inducible in the EP study 3. However in the remaining 12 patients (40%) VT/VF could again be induced despite an uneventful follow-up of 13 ± 10.2 months (median 6.5 months, range 6 to 31 months). In four patients the induced VT differed in morphology: three VTs were different in QRS axis and one VT was polymorphic. In one patient with SCD and VF in the baseline

stimulation again VF was inducible despite complete suppression in the initial drug study with sotalol. As outlined in Table 1, the two groups of reinducible and noninducible patients did not differ significantly with respect to age, heart disease, follow-up time or ejection fraction. The sotalol dosage tended to be higher with 440 ± 138 mg as compared with 364 ± 132 mg in the group with reinducible VT/VF but without reaching statistical significance. Regarding the primary arrhythmia, there were more patients with aborted SCD among the group with reinducible VT/VF ($p = 0.39$). However all patients of this group had reproducible VT in the baseline EP study 1. The extrastimuli required for reinduction as compared with the extrastimuli utilized in the baseline stimulation are illustrated in Table 2. As illustrated, a total of seven patients required more extrastimuli in the EP study 3 as compared with the EP study 1. Five patients required fewer or the same number of extrastimuli to induce VT/VF as compared with the initial study.

Follow-up after EP study 3 during long-term sotalol therapy. After the EP study 3, all patients continued the treatment with sotalol and were further followed for 22.1 ± 10.9 months (median 22.5, range 2 to 37 months). Three patients with reinducible arrhythmias wanted cardioverter-defibrillator implantation, which was subsequently performed. All these patients remained without discharges from the devices.

Five patients (17%) experienced documented monomorphic VT recurrences during the follow-up period. Noninvasive tests did not reveal any progress of the underlying cardiac disease. Among this group, four patients were again noninducible; one was reinducible in the EP study 3. All other 25 patients remained free of arrhythmia recurrences; no SCD occurred. As illustrated by Figure 2, survival free from recurrent VT did not differ significantly between the two groups.

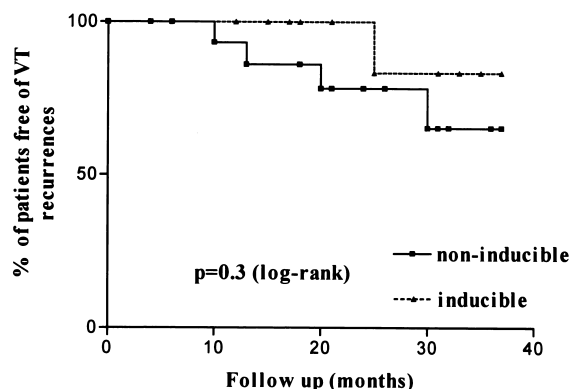


Figure 2. Curve comparison of patients with sustained ventricular tachycardia (VT) recurrences: patients with again inducible VT in electrophysiologic study 3 versus patients with noninducible VT.

DISCUSSION

Main findings. The purpose of this study was to prove the long-term reproducibility of VT/VF suppression by sotalol in electrophysiologic testing. Of 30 patients, who were all treated clinically efficiently by sotalol, 40% were reinducible in a PVS which was performed 13 ± 10 months after the initial successful drug test. The further outcome of the patients did not differ in terms of VT recurrences, although all patients were kept on sotalol irrespective of the inducibility in EP study 3. This study shows clearly the lack of long-term reproducibility of drug testing with sotalol and the minor clinical significance of inducibility or noninducibility in late EP testing under sotalol, which is clinically effective during long-term treatment.

The analysis of the outcome of all screened 78 patients resulted in a high VT/VF recurrence rate of 27% despite the fact that all patients were initially suppressible by sotalol.

Reproducibility of serial drug testing. Our study results are in agreement with some studies that have shown a high variability of short-term reproducibility of drug trials; Kundenchuk et al. (18) found a day-to-day variability of nearly 23% of initially successful drug studies in patients with coronary artery disease. In 18% of patients with VT/VF unrelated to coronary artery disease, VT/VF could again be induced in a second study 48 h after an initial effective study (19). Fogoros et al. demonstrated that even in 62% of initially successful drugs VT was inducible in repeat trials (20). The authors performed the identical stimulation protocol six times with the initially successful drug at 2 days. It was concluded that inducibility of VT/VF appeared to be a probability function, which had already been confirmed before by Cooper et al., who showed an increase of the sensitivity of arrhythmia induction during baseline testing with simple repetition of extrastimuli (24).

Temporal variability of the arrhythmogenic substrate? The proved high temporal variability of responses on PVS (14,16,17) could be explained by the fact that arrhythmias

induced by PVS might define at best the arrhythmogenic potential of a given substrate at the time the test is performed (25). Because the arrhythmogenic substrate is subject to a wide variety of pathophysiologic changes, drug effectiveness predicted by PVS might change with time. We tried to exclude any instability of the arrhythmogenic substrate in our patients, performing noninvasive tests and relying on the clinical history of the patient, which both suggested a stable clinical disease. Most of our patients presented a presumably stable substrate with a history of coronary heart disease and old myocardial infarctions; however, six patients did not have any structural heart disease with a less stable arrhythmogenic substrate. In these patients VT, was harder to induce than in others, which might have an influence on the reproducibility of arrhythmia induction in later drug tests (15). However, these patients did not differ significantly with respect to the reinducibility in the later EP study compared with the patients with underlying heart disease.

The reinducibility of VT/VF in our patients who were clinically effectively treated with sotalol did not have any prognostic impact. This discrepancy may be explained by the fact that PVS is a completely unphysiologic test with characteristics like stimulus strengths and short coupling of extrastimuli, which cannot be individually matched with the patient's substrate to ensure that an elicited response is always clinically relevant (26). Results of PVS may therefore underestimate the real clinical efficacy of sotalol, as shown by our study, because the true positive or false positive test results cannot be recognized by the response to PVS.

Trials using electrophysiologic guidance of sotalol therapy. The fact that the arrhythmia recurrence rate in the first year in the ESVEM trial was as high as 21% to 44% for sotalol and class I agents suggests a relatively weak predictive accuracy for PVS (3). Also, other trials that tested the long-term efficacy of sotalol guided by PVS reported a high relapse rate of sotalol despite complete suppression during serial drug testing, which is also confirmed by the high relapse rate of all our screened patients primarily effectively treated with sotalol (4,27,28). Recently Haverkamp et al. reported that despite the fact that suppression of inducibility of VT/VF by sotalol predicted a favorable outcome, PVS failed to predict freedom from SCD during long-term sotalol therapy (9). Also, Brugada et al. found that the clinical efficacy of a drug did not necessarily correspond to the results of serial drug testing (21,22). A small trial reported that the outcome of patients treated with sotalol for VT/VF was independent of inducibility in terms of nonfatal VT recurrences (29). Recently we reported the long-term outcome of 146 consecutive patients with inducible VT/VF (30). Ninety-nine patients with inducible VT/VF during sotalol treatment received an implantable cardioverter-defibrillator (ICD) and then were randomly assigned to therapy with sotalol or to no antiarrhythmic therapy. In the remaining 53 patients, sotalol prevented

induction of VT/VF and patients were discharged on oral sotalol. After a follow-up of approximately 33 months, the groups treated with sotalol alone or with ICD/sotalol experienced significantly less VT recurrences, with 23% and 30% respectively, compared with 51% in the ICD alone group. The recurrence rate between the sotalol and ICD/sotalol groups was not significantly different, although sotalol did not prevent the induction of VT/VF in the latter group (30). Furthermore, the recurrence rate of patients treated with ICD/sotalol is comparable to studies in which sotalol was only given in the case of complete VT/VF suppression (4,27,28).

The ESVEM trial. In the ESVEM trial, sotalol was more effective during follow-up than various class I antiarrhythmic drugs, although EP testing and Holter monitoring would have predicted similar efficacy (2,31). This suggests that it was the properties of sotalol that were responsible for this difference, rather than the techniques by which sotalol was selected for long-term therapy (25). The ESVEM trial and the results of our study stress the significance of drug-specific responses rather than a technique specificity of responses for the treatment of VT/VF (26). Therefore PVS contains various shortcomings regarding the guidance of the therapy with sotalol, a complex substance exerting class III and beta-adrenergic blocking effects (32).

In summary, we showed that in 40% of patients with a stable cardiac disease and without arrhythmia recurrences during long-term sotalol therapy, it was possible to reinduce VT/VF. Seventeen percent of all patients experienced non-fatal VT recurrences during the further follow-up period of 22 ± 11 months. This was independent of VT/VF inducibility in the EP study 3. Thus the reinducibility of VT/VF during effective long-term treatment with sotalol did not have any prognostic impact in terms of arrhythmia recurrences as compared with that in patients whose VT/VF could be again completely suppressed.

Study limitations. We decided to use stringent efficacy criteria for the drug test, using three extrastimuli in all patients regardless of the mode of induction in the baseline state, because Beckman et al. showed a significant day-to-day variability in the number of extrastimuli required for VT induction (11). We wanted to limit eventual false positive results of the drug test (33), but we had to expect a higher rate of VT/VF reinduction in the follow-up EP study using three extrastimuli in all patients. In concordance, there was a tendency toward the requirement of more extrastimuli to reinduce VT/VF after long-term sotalol treatment as compared with the number of extrastimuli required to induce VT/VF in the baseline EP study. However, this difference did not reach statistical significance.

To determine the value of PVS in guiding therapy with sotalol in patients with VT/VF, a different study design would have been more adequate; patients with suppressible and nonsuppressible VT/VF should have been included into the study and late EP testing should have been performed in

all patients including patients with VT/VF recurrences during the study period. This kind of study protocol would have necessitated an ICD as backup for ethical reasons. However, at the time the study protocol was designed, the therapy guidelines of VT/VF were different from the guidelines used nowadays.

Conclusions. This study shows that there is discordance between immediate and late EP testing during sotalol therapy. Despite an uneventful clinical follow-up in terms of VT/VF recurrences, late EP testing showed a VT/VF inducibility in a high proportion of patients. Hence, EP testing performed late after the initial drug test may no longer be predictive of outcome.

Reprint requests and correspondence: Dr Christian Mewis, Department of Cardiology, University Hospital Tübingen, Otfried-Müller-Str. 10, 72076 Tübingen, Germany.

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